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(54) Title: METHODS OF TREATING SHORT STATURE DISORDERS RELATED TO THE SHORT STATURE HOMEBOX-CONTAINING (SHOX) GENE

(57) Abstract: The invention relates to methods and articles of manufacture for treating short stature disorders related to the Short Stature Homeobox-containing (SHOX) gene which, in the human genome, is located in the pseudoautosomal region (PAR1) on the short arm of the X chromosome (Xp22.3) and Y chromosome (Yp11.3). More particularly, the invention relates to methods for treating a SHOX gene disorder, other than Turner syndrome, due to deficiency of one copy (haploinsufficiency) of the SHOX gene, by administering a growth hormone, particularly by administering human growth hormone to a human subject with a SHOX gene disorder.

WO 01/34181 A2

**METHODS OF TREATING SHORT STATURE DISORDERS RELATED TO  
THE SHORT STATURE HOMEBOX-CONTAINING (SHOX) GENE**

5

**TECHNICAL FIELD**

This invention relates to methods for treating short stature disorders related to the Short Stature Homeobox-containing gene – the SHOX gene - located in the pseudoautosomal region (PAR1) on the short arm of the X chromosome (Xp22.3) and Y chromosome (Yp11.3). More particularly, the invention relates to methods for treating a SHOX gene disorder, other than Turner syndrome, due to deficiency of one copy (haploinsufficiency) of the SHOX gene, by administering a human growth hormone.

**BACKGROUND OF THE INVENTION**

The Short Stature Homeobox-containing (SHOX) gene is located in the pseudoautosomal region (PAR1) on the short arm of the X chromosome (Xp22.3) and Y chromosome (Yp11.3) (Rao et al. 1997a). Deletion or mutation of the SHOX gene has been found in a number of patients with short stature, either idiopathic, or associated with Leri-Weill syndrome (Rao et al. 1997a; Belin et al. 1998, Shears et al 1998). Patients with Turner syndrome have absence or structural abnormalities of one X chromosome. Thus, when the deficiency involves the short arm of the X chromosome, they are haploinsufficient for the SHOX gene. Deficiency of the product of the SHOX gene is believed to be the underlying cause of growth impairment in patients with Turner syndrome. (Rao et al. 1997b; Ellison et al. 1997).

More particularly, Turner syndrome is one of the most common genetic disorders with a prevalence of approximately 1 in 2500 liveborn females. One of the cardinal features is extreme short stature of more than 20 cm below the mean height of healthy adult women. Mean adult height of women with Turner syndrome ranges between 136.7 cm (Japan) and 146.9 cm (Germany) (Lyon et al. 1985; Hibi et al. 1991; Ranke 1992). Most subjects suffer from gonadal dysgenesis with only a small percentage passing through puberty normally. In addition, many subjects show characteristic dysmorphic features with variable phenotypic penetrance, such as

broad chest with widely spaced nipples, low posterior hairline, webbed neck, lymphedema, hyperconvex nails, and multiple cutaneous nevi. Renal and cardiac defects are also common.

Turner syndrome is caused by the lack of or an alteration in one X chromosome. The most frequent karyotype is 45,X, while other subjects show 45,X/46,XX mosaicism, 46,X,i(Xq), 45,X/46,X,i(Xq), and other X chromosomal abnormalities. Recently, it was demonstrated that a gene located in the pseudoautosomal region (PAR1) at the tip of the short arm of the X chromosome (Xp22.3) is related to short stature in Turner syndrome. This gene was termed "short stature homeobox gene" (SHOX) (Rao et al. 1997b). Independently, the same gene was identified by a different group and was termed pseudoautosomal homeobox-containing osteogenic gene (PHOG) (Ellison et al. 1997). The SHOX gene encodes a homeodomain-containing protein that most likely functions as a transcription regulator. Dosage sensitivity is a common feature of such regulatory genes in the pseudoautosomal region. They escape X inactivation and have functional homologs on the Y chromosome (Zinn et al. 1993; Bardoni et al. 1994; Disteche 1995). For this and other reasons, it is hypothesized that haploinsufficiency of the SHOX gene is the underlying cause of growth impairment in subjects with Turner syndrome (Rao et al. 1997; Ellison et al. 1997). A number of skeletal abnormalities found in patients with Turner syndrome may be associated with reduced SHOX expression during embryogenesis such as abnormal lower-to-upper leg/arm ratio (90%), micrognathia (60%), cubitus valgus (45%), high-arched palate (35%), short metacarpals (35%), genu valgum (30%), scoliosis (12%), and Madelung deformity (7%) (Lippe 1991).

SHOX mutations and deletions have also been detected in short-statured subjects of both genders without Turner syndrome (Rao et al. 1997b; Shears et al. 1998; Belin et al. 1998). Methods for screening for SHOX gene defects are described, for instance, in Rao et al., 1997a and 1997b, and in published PCT application WO 98/14568, published April 9, 1998, which is hereby incorporated herein by reference. The phenotype in these subjects was variable. Some subjects were unaffected by morphological abnormalities while others are affected by a

specific form of skeletal dysplasia known as Leri-Weill syndrome. Leri-Weill syndrome (Leri-Weill dyschondrosteosis) is an autosomal-dominant disorder with a more pronounced phenotype in females than in males (Léri and Weill 1929; Jones 1988). The most frequent abnormalities are small stature with an adult height ranging from 135 cm to normal, short forearm with Madelung deformity, and short lower leg. Most subjects with Madelung deformity (Madelung 1878), a characteristic malformation of the wrist ("dinner-fork" deformity) which is also found in up to 10% of subjects with Turner syndrome, have Leri-Weill dyschondrosteosis (Jones 1988). The homozygous form of this disorder is called Langer mesomelic dysplasia, a rare syndrome marked by extreme short stature and severe skeletal dysplasia (Langer 1967; Jones 1988). In accordance with the pseudoautosomal dominant mode of inheritance, haploinsufficiency of the SHOX gene is also thought to be the cause of short stature in subjects with Leri-Weill syndrome as it is in Turner syndrome (Rao et al. 1997a). Based on preliminary data produced by the present inventors, the prevalence of SHOX disorder, not associated with Turner syndrome, is estimated to be approximately 1:5,000 in both sexes.

The growth hormones from man and from the common domestic animals are proteins of approximately 191 amino acids, synthesized and secreted from the anterior lobe of the pituitary gland. Human growth hormone consists of 191 amino acids. Growth hormone is a key hormone involved in the regulation of not only somatic growth, but also in the regulation of metabolism of proteins, carbohydrates and lipids. The major effect of growth hormone is to promote growth. The organ systems affected by growth hormone include the skeleton, connective tissue, muscles, and viscera such as liver, intestine, and kidneys.

Over the past ten years, studies conducted by a number of manufacturers of somatropin (recombinant human growth hormone, rhGH) have demonstrated that rhGH is effective in increasing the final height of subjects with Turner syndrome (Donaldson 1997; Plotnick et al. 1998; Rosenfeld et al. 1998; Carel et al. 1998; Quigley et al. 1998). In general, treatment was safe. Turner syndrome has been registered as an approved indication of somatropin therapy worldwide in most countries, including the United States, based on data that show an increase in growth

velocity and an improvement of final height. The cause of short stature in Turner syndrome and in other subjects with SHOX defect with or without skeletal dysplasias (SHOX disorder) is haploinsufficiency of the SHOX gene (Rao et al. 1997b; Ellison et al. 1997).

5           Since somatropin is effective in treatment of short stature associated with SHOX disorder in subjects with Turner syndrome, the present inventors have hypothesized that somatropin therapy is also effective in improving growth rate and final height in subjects with SHOX disorder who do not have Turner syndrome.

          Schwarze CP et al., Horm Res 51 (suppl 2):P87 (1999), discloses SHOX  
10   gene mutations in children with idiopathic short stature, including screening and therapy with rhGH in two children. Vuguin P et al., Growth Hormone IGF Res 8(4):abstract O-30 (1998), discloses the effect of growth hormone treatment of one subject with idiopathic short stature with SHOX mutation. Shanske A. et al., Am J Med Genet 82(1):34-9 (Jan 1, 1999) discloses a deletion of the pseudoautosomal  
15   region in a male with a unique Y;13 translocation and short stature, including treatment with recombinant growth hormone.

### **SUMMARY OF THE INVENTION**

          The present invention relates to a method for treating short stature in a  
20   subject having a SHOX gene disorder other than Turner syndrome. This method comprises administering to such a subject a pharmaceutically active amount of a growth hormone. In a preferred embodiment of this method, the subject is a human subject and the growth hormone is human growth hormone.

          The invention also provides an article of manufacture comprising packaging  
25   material and a pharmaceutical composition comprising a growth hormone contained within the packaging material. This pharmaceutical composition is therapeutically effective for treatment of short stature due to a SHOX gene disorder other than Turner syndrome, and the packaging material comprises a label which indicates that the growth hormone can be administered to a subject with a SHOX gene disorder  
30   other than Turner syndrome. In a preferred embodiment of this article of manufacture the growth hormone is human growth hormone.

The invention further provides an article of manufacture comprising packaging material and a pharmaceutical composition comprising a growth hormone contained within said packaging material, where the pharmaceutical composition is therapeutically effective for treatment of short stature due to a SHOX gene disorder other than Turner syndrome. This packaging material comprises a label which indicates that the growth hormone is effective in increasing growth velocity of subjects with a SHOX gene disorder other than Turner syndrome. In a preferred embodiment of this article of manufacture the growth hormone is human growth hormone.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 shows the plan for clinical trial, described below in Example 1, conducted to compare the mean growth rate of a group of subjects with SHOX disorder who receive human growth hormone therapy with the mean growth rate of subjects who receive no human growth hormone (nontreatment control).

#### **DETAILED DESCRIPTION**

The invention relates to a method of to a method for treating short stature in a subject having a SHOX gene disorder other than Turner syndrome, which method comprises administering to such a subject a pharmaceutically active amount of a growth hormone, particularly in a human subject, administering human growth hormone.

As used herein, a "subject having a SHOX gene disorder" is defined as a subject with a mutation which reduces expression or activity of a product (e.g., mRNA or polypeptide or an activity of a polypeptide, such as a binding activity) encoded by the Short Stature Homeobox-containing (SHOX) gene on at least one chromosome of the subject, which gene in the human genome is located in the pseudoautosomal region (PAR1) on the short arm of the X chromosome (Xp22.3) and Y chromosome (Yp11.3) (Rao et al. 1997a). Methods for screening for SHOX gene defects are described, for instance, in Rao et al., 1997a and 1997b, and in

published PCT application WO 98/14568, published April 9, 1998, which is hereby incorporated herein by reference. The mutation may comprise a deletion or other mutation of all or any part of the SHOX gene, as identified by DNA analysis or other appropriate molecular technique, or a mutation elsewhere in the genome of the subject which nevertheless reduces expression and/or activity of a SHOX gene product. Subjects with SHOX disorder include those with and without Leri-Weill syndrome.

Subjects with Turner syndrome are defined as follows: Females whose karyotype contains a documented abnormality of the X chromosome involving the short arm (for example, 45,X; 46,X,Xp-; 46X,i[Xq]). Female subjects with a partial deletion of the short arm of the X-chromosome are not defined as having Turner syndrome, if the deletion is located distal to the gene for ocular albinism (OA1) at the junction between Xp22.2 and Xp22.3. Instead, they are defined as having SHOX disorder (Ballabio and Andrea 1992). Although subjects with Turner syndrome are deficient in one SHOX allele, for the purpose of the present application, females with a karyotype abnormality characteristic of Turner syndrome are not included in the subject population specifically defined as having SHOX disorder. Based on preliminary data produced by the present inventors, the prevalence of SHOX disorder, not associated with Turner syndrome, is estimated to be approximately 1:5,000 in both sexes.

In addition, a subject having a "SHOX gene disorder" as defined herein also has an abnormally short stature, according to standard measures known in the art, such as may be observed in subjects with growth hormone deficiency. However, subjects having a SHOX gene disorder are not growth hormone deficient by standards known in the art. For instance, for treatment in the clinical trial described in Example 1, below, a subject with a SHOX gene disorder has a peak growth hormone level greater than 7 ng/mL or 14 mU/L. For treatment as described in Example 1, a subject with a SHOX gene disorder is considered to have abnormally short stature if the subject has a chronological age of at least 3 years, bone age of less than 10 years for boys and less than 8 years for girls, and height below the 3rd percentile or height below the 10th percentile and growth velocity below the 25th

percentile, for an appropriate age-and-sex-matched 'normal' reference population based upon local standards. For this exemplary study, subjects with a SHOX disorder also are prepubertal (for girls, Tanner stage 1 with respect to breast development; for boys, Tanner stage 1 with respect to genital development and testicular volume of no more than 2 ml).

#### Administering Growth Hormone

In the present context "growth hormone" may be growth hormone from any origin such as avian, bovine, equine, human, bovine, porcine, salmon, trout or tuna growth hormone, preferably bovine, human or porcine growth hormone, human growth hormone being most preferred. The growth hormone used in accordance with the invention may be native growth hormone isolated from a natural source, e.g. by extracting pituitary glands in a conventional manner, or a growth hormone produced by recombinant techniques, e.g. as described in E. B. Jensen and S. Carlsen in *Biotech and Bioeng.* 36, 1-11 (1990). The "growth hormone" may also be a truncated form of growth hormone wherein one or more amino acid residues has (have) been deleted; an analogue thereof wherein one or more amino acid residues in the native molecule has (have) been substituted by another amino acid residue, preferably a natural amino acid residue, as long as the substitution does not have any adverse effect such as antigenicity or reduced action; or a derivative thereof, e.g. having an N- or C-terminal extension such as Met-hGH. The preferred growth hormone is hGH.

The term "dose" of growth hormone refers to that amount that provides therapeutic effect in an administration regimen. The growth hormone is formulated for administering a dose effective for increasing growth rate of a subject having a SHOX gene disorder other than Turner syndrome, for instance, a dose similar to one effective for increasing growth in a Turner syndrome subject. Such doses for Turner syndrome are known in the art. See also Example 1, below, for preferred dosages in the method of the invention.

In general, formulations for parenteral administration are prepared containing amounts of hGH at least about 0.1 mg/ml, preferably upwards of about 10 mg/ml, preferably from about 1 mg/ml to about 40 mg/ml, more preferably from about 1



mg/ml to about 25 mg/ml, e.g. from 1 mg/ml to about 5 mg/ml, calculated on the ready-to-use formulation. For use of these compositions in administration to human beings suffering from SHOX disorder, for example, these formulations contain from about 0.1 mg/ml to about 10 mg/ml, corresponding to the currently contemplated dosage regimen for the intended treatment. The concentration range is not critical to the invention and may be varied by the physician supervising the administration.

A growth hormone can typically be administered parenterally, preferably by subcutaneous injection, by methods and in formulations well known in the art. A growth hormone can be formulated with typical buffers and excipients employed in the art to stabilize and solubilize proteins for parenteral administration. See, for example, United States Patent No. 5,612,315 to Pikal, et al., hereby incorporated herein by reference, disclosing pharmaceutical growth hormone formulations, and United States Patent No. 5,851,992 to Sørensen et al., incorporated herein by reference, disclosing human growth hormone formulations which may be used to treat a patient with a disorder associated with growth hormone deficiency. Art recognized pharmaceutical carriers and their formulations are described in Martin, "Remington's Pharmaceutical Sciences," 15th Ed.; Mack Publishing Co., Easton (1975). A growth hormone can also be delivered via the lungs, mouth, nose, by suppository, or by oral formulations, using methods known in the art.

The hormone can be administered regularly (e.g., once or more each day or week), intermittently (e.g., irregularly during a day or week), or cyclically (e.g., regularly for a period of days or weeks followed by a period without administration). Preferably growth hormone is administered once daily for at least about one year, more preferably at least about three years, and most preferably for at least about six or seven years.

#### Articles of Manufacture

The present invention also encompasses articles of manufacture comprising packaging material and a pharmaceutical composition comprising a growth hormone contained within the packaging material. This pharmaceutical composition is therapeutically effective for treatment of short stature due to a SHOX gene disorder

other than Turner syndrome, and the packaging material comprises a label which indicates that the growth hormone can be administered to a subject with a SHOX gene disorder other than Turner syndrome.

For instance, an article of manufacture of this invention may comprise a kit including pharmaceutical compositions to be used in the methods of the present invention. The kit can contain a container, such as a vial or cartridge for an injection pen, which contains a formulation of growth hormone and suitable carriers, either dried or in liquid form. The kit further includes instructions in the form of a label on the vial or cartridge and/or in the form of an insert included in a box in which the vial or cartridge is packaged, for the use and administration of the growth hormone composition. The instructions can also be printed on the box in which the vial or cartridge is packaged. The instructions contain information such as sufficient dosage and administration information so as to allow a worker in the field or a human subject to administer the drug, as is customary in most locales.

The example which follows are illustrative of the invention and are not intended to be limiting.

### **EXAMPLES**

#### **Example 1 - -Increased Growth Rate of Subjects with SHOX Disorder Treated with Human Growth Hormone**

A clinical trial of one year duration is conducted to compare the mean growth rate of a group of subjects with SHOX disorder who receive human growth hormone therapy with the mean growth rate of subjects who receive no human growth hormone (nontreatment control). A secondary objective is to compare the mean growth rate of growth hormone-treated subjects with SHOX disorder with that of a group of growth-hormone-treated subjects with Turner syndrome, using a non-inferiority analysis.

At the conclusion of the one year acute phase of the study, all patients, both in the growth hormone-treated and untreated groups, are asked to participate in the extension period. For the first year of the extension they receive the same therapy as in the acute phase period. That is, patients with SHOX disorder randomized to the

non-treatment arm continue to be monitored without receiving growth hormone, while those randomized to the treatment arm continue to receive growth hormone. After one year in the extension phase all patients are given the option to receive growth hormone for an additional 2-year extension period, during which they are monitored for efficacy and safety.

More in particular, this study is designed to show that mean first-year growth velocity of patients with SHOX disorder who receive human growth hormone (0.05 mg/kg/day) is significantly greater than that of patients with SHOX disorder who do not receive human growth hormone. The study is divided into four periods: the Screening Period; the Acute Therapy Period, the Extension Therapy Period A and the Extension Therapy Period B. During the Screening Period, patients who fulfil the screening criteria undergo analysis of the SHOX gene. Those with either deletion or mutation of the SHOX gene are potentially eligible for study entry. Patients with proven SHOX gene defects and those with Turner syndrome who do not have evidence of growth hormone deficiency (based on serum concentrations of IGF-I and IGFBP-3 and, if necessary, a growth hormone stimulation test) are eligible for study entry. Patients with SHOX disorder who meet entry criteria are randomized at study entry into one of two therapy groups – human growth hormone therapy or non-treatment control. All eligible and consented patients with Turner syndrome receive growth hormone therapy. Efficacy and safety information to be used for registration are collected during the Acute Therapy Period. After one year on study, all patients (treatment and control) participate in the extension. In the first year of the extension, (Extension Part A) treatment is continued exactly as in the acute phase. Thereafter, in Extension Part B, all patients receive human growth hormone and monitoring of efficacy and safety is continued.

About 50 subjects are given human growth hormone during the first year of this clinical trial, about twenty five having Turner syndrome and about 25 having SHOX disorder. The remaining about 25 patients with SHOX disorder are randomized to the non-treatment control group.

**Summary of Study Design**

As illustrated in Figure 1, the study is divided into periods: Screening, Acute Therapy, and Extension, Parts A and B.

**Screening Period:** Turner syndrome subjects are screened to determine that they do not have growth hormone deficiency; non-Turner syndrome subjects are screened to determine that they have SHOX disorder and are not growth hormone deficient.

**Acute Therapy Period:** After screening, subjects with SHOX disorder are randomized in a 1:1 ratio to either the SHOX disorder somatropin-treatment group or the SHOX disorder nontreatment group. Subjects with Turner syndrome are entered into the Turner syndrome somatropin-treatment group. During this period, subjects in the somatropin treatment groups receive a daily subcutaneous injection of 0.05 mg/kg of somatropin for 1 year. Subjects in the nontreatment control group receive no injections. Subjects in each group are followed at defined intervals for 1 year as outlined below.

**Extension, Part A:** Following the Acute Therapy period, all subjects have the option to participate in the Extension. During Extension Part A, subjects continue in their treatment groups assigned during the Acute Therapy Period. Subjects in each group are followed at defined intervals for 1 year as outlined below.

**Extension, Part B:** After completion of Extension Part A, all subjects are given the option to receive somatropin treatment in Extension Part B. Both those who choose somatropin therapy and those who elect not to receive somatropin therapy are monitored in Extension Part B. Study drug is provided for 2 years during Extension Part B.

Design and ControlVisit Schedule

Visit 0	Screening
Visit 1	Randomization
Visit 2	3 months $\pm$ 3 weeks after Visit 1
Visit 3	6 months $\pm$ 4 weeks after Visit 1
Visit 4	12 months $\pm$ 4 weeks after Visit 1
Visit 101	18 months $\pm$ 4 weeks after Visit 1
Visit 102	24 months $\pm$ 4 weeks after Visit 1
Visit 201 <sup>a</sup>	3 months $\pm$ 3 weeks after Visit 102
Visit 202 to Visit 205	Every 6 months $\pm$ 4 weeks after Visit 102 for 2 years

<sup>a</sup> Only previously untreated subjects who commence somatropin therapy at Visit 102 require a Visit 201.

5

Screening

According to local requirements, the subject's parents/legal guardians sign Informed Consent Document(s) before any procedures are performed. All screening blood specimens for central laboratory analysis (IGF-I and IGFBP-3; SHOX gene analysis as applicable) are drawn. Anthropometry and background information are collected and recorded on the Clinical Report Forms (CRFs).

10

Blood samples from subjects without Turner syndrome are shipped to a central lab for SHOX screening. Methods for screening for SHOX gene defects are described, for example, in Rao et al., 1997a and 1997b, and in published PCT application WO 98/14568 which is hereby incorporated herein by reference.

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All subjects without Turner syndrome undergo SHOX analysis whether or not it has been previously performed. As outlined below in Parent/Sibling Information, it may be necessary to obtain and test parent blood to confirm diagnosis of SHOX disorder.

20

IGF-I and IGFBP-3 determinations are performed only for subjects with confirmed Turner syndrome or confirmed SHOX disorder (either previously diagnosed or confirmed by the central lab). Subjects with IGF-I levels greater than  $-2.0$  SD or IGFBP-3 levels greater than  $-1.6$  SD, as determined by the central lab, proceed to Visit 1. Subjects with IGF-I levels less than or equal to  $-2.0$  SD and

IGFBP-3 levels less than or equal to  $-1.6$  SD undergo a growth hormone stimulation test (local laboratory testing). The stimulus used is at the discretion of the investigator. Subjects who are not growth hormone deficient (peak growth hormone level greater than 7 ng/mL or 14 mU/L) are eligible to proceed to Visit 1.

5 Parental height is measured when possible.

#### **Acute Therapy**

Following baseline data collection, subjects with SHOX deficiency are randomized to one of two treatment groups – the somatropin treatment group or the nontreatment control group. All subjects undergo collection of blood samples for  
10 central laboratory analysis of alkaline phosphatase and Pro-collagen I C-terminal Peptide (PICP). In addition, these subjects are given a urine collection kit and instructions to collect urine at approximately 1 month after the start of somatropin therapy. Baseline hand/wrist, forearm, and lower leg x-rays are performed to further evaluate the SHOX disorder phenotype and to determine bone ages. Additional  
15 procedures are performed as needed for analysis of efficacy and safety.

#### **Extension Part A**

Hand/wrist, forearm, and lower leg x-rays are performed to further evaluate the SHOX disorder phenotype and to determine bone ages.

#### **Extension, Part B**

20 The intent of the Extension Part B is to monitor subjects for safety and efficacy for 2 years. After this 2-year period, each subject is asked to participate in a long-term surveillance study, for continued monitoring.

#### **Parental/Sibling Information**

In some subjects, analysis of their chromosomes or DNA may be sufficient  
25 to confirm diagnosis of SHOX disorder. However, in other subjects with different abnormalities in the SHOX gene (e.g. missense mutations) analysis of parental chromosomes may be helpful in clarifying the genotype/phenotype correlation in SHOX disorder. Therefore, parents may be asked to provide blood samples during the screening phase.

30 After confirmation of SHOX disorder, parents (who have not had blood drawn during screening) and siblings of subjects meeting entry criteria are asked to

provide blood samples to further understand the genetics of SHOX gene deletions and mutations. Samples from family members will be collected before Visit 4, if possible.. Where appropriate, DNA sequencing of the SHOX genes is performed. In addition, anthropometric data and presence or absence of dysmorphic signs are collected.

### Inclusion Criteria

Subjects may be included in the study only if they meet all of the following criteria:

- 10 [1] Turner syndrome or SHOX disorder as defined below.
- [2] Chronological age of at least 3 years.
- [3] For subjects with SHOX disorder, bone age of less than 10 years for boys and less than 8 years for girls. For girls with Turner syndrome, bone age of less than 9 years.
- 15 NOTE: If bone age was not obtained at a time close to study entry, the approximate current bone age is estimated based on the most recent X-ray, performed and assessed locally, within 12 months prior to study entry. For example, if the child's bone age was determined 6 months prior to study entry to be 8.0 years, then
- 20 the bone age to be used for assessment of potential inclusion in the study would be 8.5 years.
- [4] Height below the 3rd percentile  
or  
height below the 10th percentile and growth velocity below the
- 25 25th percentile, for an appropriate age-and-sex-matched 'normal' reference population based upon local standards.
- [5] Prepubertal: For girls, Tanner stage 1 with respect to breast development. For boys, Tanner stage 1 with respect to genital development and testicular volume of no more than 2 ml.

### Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

- 5 [6] Langer syndrome (or Langer mesomelic dysplasia, a homozygous form of Leri-Weill syndrome)
- [7] Known growth hormone deficiency as defined by IGF-I levels less than or equal to  $-2.0$  SD and IGFBP-3 levels less than or equal to  $-1.6$  SD below the age-dependent mean and peak growth hormone level less than 7 ng/mL, in response to a pharmacologic stimulus.
- 10 [8] Known growth hormone receptor defect as defined by a score system (Blum et al. 1994).

### Disease Diagnostic Criteria

15 For the purposes of this study subjects with SHOX disorder are defined as follows:

Subjects with a mutation or deletion in the SHOX gene as identified by DNA analysis or other appropriate molecular technique. Subjects with SHOX disorder include those with and without Leri-Weill syndrome.

Subjects with Turner syndrome are defined as follows:

20 Females whose karyotype contains a documented abnormality of the X chromosome involving the short arm (for example, 45,X; 46,X,Xp-; 46X,i[Xq]). Female subjects with a partial deletion of the short arm of the X-chromosome are not classified as having Turner syndrome, if the deletion is located distal to the gene for ocular albinism (OA1) at the junction between Xp22.2 and Xp22.3. Instead, they are

25 diagnosed as having SHOX disorder (Ballabio and Andrea 1992).

Although subjects with Turner syndrome are deficient in one SHOX allele, for the purpose of this study, females with a karyotype abnormality characteristic of Turner syndrome are not included in the subject population specifically designated as having SHOX disorder. These subjects continue to receive the standard



designation of Turner syndrome, and are eligible for inclusion in the Turner syndrome group only.

#### Dosage and Administration

##### Materials and Supplies

5 Somatropin is provided in disposable cartridges of lyophilized study drug (Somatropin, rDNA origin, for injection, Eli Lilly and Company, Indianapolis, IN, USA) for use with the HumatroPen™. However, if the HumatroPen is locally unavailable, disposable vials for reconstitution by standard methods are provided. Each cartridge contains 6.0 mg, 12.0 mg, or 24 mg of somatropin; vials contain 5.0  
10 mg somatropin. Cartridges or vials of diluent for reconstitution are provided with the cartridges or vials of somatropin, as appropriate. Detailed instructions and appropriate supplies required for mixing and administration of study material are also be provided.

##### Dosage Administration

15 Somatropin will be administered as follows: a single daily subcutaneous injection, preferably before bedtime, at a dose of 0.05 mg/kg/day, rounded appropriately.

#### Efficacy Evaluations

##### Efficacy

20 The primary measure of efficacy is standing height. This is measured at each visit throughout the study, preferably at the same time of day. All measurements are made without shoes. Standing measurements are made using a standard wall-mounted stadiometer. The instrument should be calibrated using a standard calibration rod, to at the start of the study and every 3 months thereafter.

25 The primary response variable to be used to assess efficacy is first-year growth velocity, defined as 1-year height minus baseline height, divided by the exact elapsed time in years (365.25 days per year is assumed throughout).

The secondary response variables used to assess efficacy are: 1) Baseline to  
1-year change in height standard deviation score, using the height of US males and  
30 females at various chronological ages as the reference standard. A standard deviation score for a given variable is derived by subtracting the age-and-sex-

matched population mean value for that variable from the subject's value. The value obtained is then divided by the age-and-sex-matched population's standard deviation (Hamill et al. 1977). 2) Baseline to 1-year change in height standard deviation score relative to mid-parental height (target height) standard deviation score. The standing heights of both parents will be required to derive this variable. 3) Second-year growth velocity.

The primary endpoint of this trial is the growth velocity (cm/year) after approximately 1 year in the study. All other efficacy criteria will be considered secondary.

## 10 Data Analysis Methods

### Sample Size

Assuming 20 subjects per arm complete the study, this sample size provides approximately 89% power for a two-sided 0.05-level test to detect a mean difference in first-year growth velocity of 2 cm between the SHOX disorder somatropin treatment and nontreatment arms, assuming the standard deviation of growth velocity in each group is 2 cm.

The primary analysis is an intent-to-treat analysis. An intent-to-treat analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

Hypothesis tests are performed at a 2-sided significance level of 0.05. Where computationally feasible, exact tests are substituted for chi-square tests.

Baseline values for the Acute Therapy Period are considered to be the initial measurements taken at Visit 1. Endpoint for the Acute Therapy Period is defined as the last non-missing measurement obtained on or prior to Visit 4.

Comparisons of treatment groups are made using least-squares means from the relevant statistical model.

In addition to the analyses described below, exploratory analyses of the data are conducted as deemed appropriate.

### Data to be Analyzed

The primary efficacy analysis includes data from all subjects with SHOX disorder with a baseline standing height measurement and a post-baseline standing height measurement at least 9 weeks past his or her Visit 1 date. (This criterion is included in order to avoid extreme extrapolation of growth velocity data.)

A secondary analysis of the primary hypothesis includes data from all subjects with SHOX disorder who have a baseline standing height measurement and a standing height measurement within 4 weeks of one year after his or her Visit 1 date, excluding any subject assigned to the somatropin-treatment arm who did not receive at least 90 days of somatropin therapy.

### Subject Characteristics

Subject characteristics (for example, demographics, baseline height standard deviation score) are summarized for all subjects entered in the study. Comparisons of subject characteristics, between the groups, are made for all randomized subjects. Frequencies are analyzed using chi-square tests. Means are analyzed using analysis of variance with treatment group (treated vs. nontreated) as the explanatory variable. Subject characteristics for the Turner syndrome arm are tabulated and reported separately.

### Efficacy Analyses

The primary question to be answered is as follows: Is the mean first-year growth velocity of SHOX disorder somatropin-treated subjects greater than that of SHOX disorder subjects not treated with somatropin? To answer this question, the data is analyzed using an analysis of covariance (ANCOVA) model. The response variable for this model is first-year growth velocity, defined as endpoint height minus baseline height, divided by the exact elapsed time in years. Explanatory variables (fixed effects) are treatment group (SHOX disorder somatropin-treatment group or SHOX disorder nontreatment group), Leri-Weill syndrome (present or absent), gender, and baseline age. (Baseline age is included because growth velocity is highly correlated with the subject's age (Hamill et al. 1977). Its inclusion in the model helps reduce residual variability and helps correct any potential baseline-age imbalances in the two groups.) The primary comparison is a comparison of least-

square means from this model, treatment compared to nontreatment. Statistical tests on other terms in the above model are not performed as part of the primary efficacy analysis. Note that the Turner syndrome arm is not included in this primary efficacy analysis.

5           A secondary analysis of the primary objective is performed using a statistical model as in the previous paragraph, but including only those subjects described above. Annualized growth velocity at Visits 2 and 3 are also analyzed, with only available data at the visit of interest included in the analysis. The response variable for a given visit is height at the given visit minus baseline height, divided by the  
10           exact elapsed time in years. These statistical models also include treatment group, Leri-Weill syndrome, gender, and baseline age as explanatory variables.

          After inspection of data regarding compliance with the protocol, further analyses are conducted if indicated based on compliance with the protocol.

          Baseline to endpoint change in height standard deviation score is also  
15           analyzed, using the height of US males and females at various chronological ages as the reference standard (Hamill et al. 1977). This analysis is performed including explanatory variables as above.

          Baseline to endpoint change in height standard deviation score relative to mid-parental height (target height) standard deviation score is also analyzed. This  
20           analysis is performed including explanatory variables as above.

          Bone ages are assessed in order to compare the rate of skeletal maturation between the SHOX disorder treated and nontreated groups.

#### **Secondary Analyses**

          To evaluate the similarity of first-year growth velocities between the two  
25           somatropin-treatment groups (SHOX disorder somatropin-treatment group compared with Turner syndrome somatropin-treatment group), a 90% two-sided confidence interval for the mean difference in growth velocity is performed. This confidence interval is based on least-squares means from the model with the response variable of first-year growth velocity and explanatory variables somatropin-treatment group  
30           and baseline age. If the lower limit of this confidence interval (SHOX disorder minus Turner) is greater than -2, this is considered to be evidence that the SHOX

disorder group's response to somatropin is not substantially less than the Turner syndrome group's response. If the lower limit of the confidence interval is less than -2 and the upper limit is greater than -2, the result is considered to be indeterminate. If the upper limit of the given confidence interval is less than -2, the conclusion is that the growth hormone treated SHOX disorder subjects grow more slowly on average than growth hormone treated Turner syndrome subjects. Further exploratory analyses are carried out to determine if there are substantial differences in growth velocity between males and females. If so, an additional analysis is carried out, comparing SHOX disorder somatropin-treated female subjects to Turner syndrome subjects. Note that the cutoff of -2 is considered to correspond to a clinically relevant difference. Also note that the above test involving the 90% confidence interval corresponds to a 0.05 level non-inferiority test.

In order to investigate the question of whether the second-year growth velocity of SHOX disorder somatropin-treated subjects greater than that of SHOX disorder subjects not treated with somatropin, the data are analyzed using an ANCOVA model with response variable of second-year growth velocity, defined as height at Visit 102 minus height at Visit 4, divided by the exact elapsed time in years. Explanatory variables (fixed effects) will be treatment group (SHOX disorder somatropin-treatment group or SHOX disorder nontreatment group), Leri-Weill syndrome (present or absent), gender, and baseline age. Subjects who have entered puberty on or prior to Visit 102 may be excluded from this analysis.

#### Subgroup Analyses

The consistency of the treatment effect (for subjects with SHOX disorder) is assessed over subgroups of subjects defined by various characteristics, including the following as examples:

- Baseline height standard deviation score (grouped appropriately, or as a continuous covariate)
- Parental origin of SHOX mutation chromosome
- Target height
- Baseline age

- Presence or absence of Leri-Weill syndrome
- Gender
- Baseline IGF-I levels (grouped appropriately, or as a continuous covariate)
- 5      • Baseline IGFBP-3 levels (grouped appropriately, or as a continuous covariate)
- Baseline height < 3<sup>rd</sup> percentile vs. ≥ 3<sup>rd</sup> percentile

A linear (possibly mixed effects) model is fitted which includes the following explanatory variables: main effects (including treatment group) and two-way interactions of the above variables with treatment group. The response variable is first-year growth velocity, calculated based on the 1-year height measurement. Appropriate parsimonious models will be developed. The relationship of each important covariate to treatment effect is assessed with the treatment-by-covariate interaction. A significant treatment-by-covariate interaction ( $P < 0.05$ ) may imply a differential treatment effect within levels of the covariate. One-year growth velocity is summarized in tables of least-square means for any interesting breakdown of the data by these subgroups.

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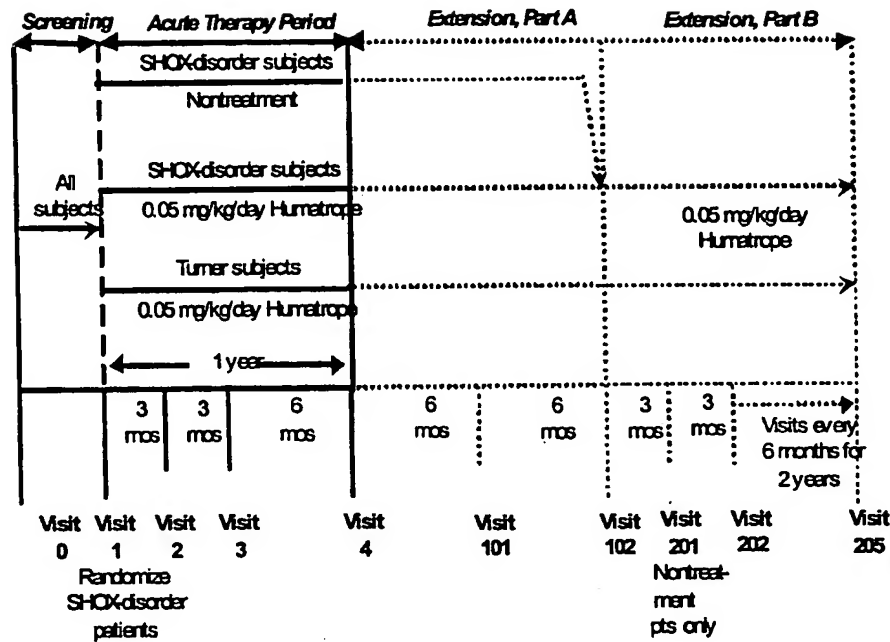
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20     The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention. All publications and patent applications in this specification are indicative of the level of ordinary skill in the art to which this invention pertains.

**WE CLAIM:**

1. A method for treating short stature in a subject having a SHOX gene disorder other than Turner syndrome, said method comprising administering to said  
5 subject a pharmaceutically active amount of a growth hormone.
2. The method according to claim 1, wherein said subject is a human subject and said growth hormone is human growth hormone.
- 10 3. An article of manufacture comprising packaging material and a pharmaceutical composition comprising a growth hormone contained within said packaging material, wherein said pharmaceutical composition is therapeutically effective for treatment of short stature due to a SHOX gene disorder other than  
15 Turner syndrome, and wherein said packaging material comprises a label which indicates that said growth hormone can be administered to a subject with a SHOX gene disorder other than Turner syndrome.
4. The article of manufacture of claim 3 wherein the growth hormone is human growth hormone.  
20
5. An article of manufacture comprising packaging material and a pharmaceutical composition comprising a growth hormone contained within said packaging material, wherein said pharmaceutical composition is therapeutically effective for treatment of short stature due to a SHOX gene disorder other than  
25 Turner syndrome, and wherein said packaging material comprises a label which indicates that said growth hormone is effective in increasing growth velocity of subjects with a SHOX gene disorder other than Turner syndrome.
6. An article of manufacture of claim 5 wherein the growth hormone is  
30 human growth hormone.

FIGURE 1



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(54) Title: METHODS OF TREATING SHORT STATURE DISORDERS RELATED TO THE SHORT STATURE HOMEBOX-CONTAINING (SHOX) GENE

(57) Abstract: The invention relates to methods and articles of manufacture for treating short stature disorders related to the Short Stature Homeobox-containing (SHOX) gene which, in the human genome, is located in the pseudoautosomal region (PAR1) on the short arm of the X chromosome (Xp22.3) and Y chromosome (Yp11.3). More particularly, the invention relates to methods for treating a SHOX gene disorder, other than Turner syndrome, due to deficiency of one copy (haploinsufficiency) of the SHOX gene, by administering a growth hormone, particularly by administering human growth hormone to a human subject with a SHOX gene disorder.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01612

## A. CLASSIFICATION OF SUBJECT MATTER

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Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SCHWARZE C P ET AL: "SHOX gene mutations in children with idiopathic short stature - screening and therapy with rhGH." HORMONE RESEARCH (BASEL), vol. 51, no. SUPPL. 2, August 1999 (1999-08), page 34 XP001002411 38th Annual Meeting of the European Society for Paediatric Endocrinology; Warsaw, Poland; August 29-September 1, 1999 ISSN: 0301-0163 cited in the application the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VUGUIN P ET AL: "The effect of growth hormone treatment in idiopathic short stature with SHOX mutation." PEDIATRIC RESEARCH, vol. 43, no. 4 PART 2, April 1998 (1998-04), page 87A XP002168567 Annual Meeting of the American Pediatric Society and the Society for Pediatric Research; New Orleans, Louisiana, USA; May 1-5, 1998 ISSN: 0031-3998 cited in the application the whole document ---	1-6
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